I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on March 24, 2008.

Frank C. Eisenschenk, Ph.D., Patent Attorney

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322 AND 1.323
Docket No. G-092US02CIP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Bernard Bihain, Barbara Bour, Lydie Bougueleret
Issued	:	May 22, 2007
Patent No.	:	7,220,581
For	:	Schizophrenia Related Gene

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE) and 1.323 (APPLICANTS' MISTAKE)

Sir:

A Certificate of Correction for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:	**Application Should Read:**
Column 7, line 59:	Page 14, line 18:
"The term "purfied" may"	--The term "purified" may--

Patent Reads:	**Application Reads:**
Column 13, line 33:	Page 25, line 4:
"nucleofide sequence"	--nucleotide sequence--
Column 13, line 36:	Page 25, line 5:
"nucleofide sequence"	--nucleotide sequence--

Patent Reads:	**Application Should Read:**
Column 29, line 44:	Page 55, line 7:
"the PAPAP poypeptide"	--the PAPAP polypeptide--
Column 30, line 27:	Page 56, line 15:
"systems is used"	--systems are used--
Column 30, line 36:	Page 56, line 21:
"fragments is produced"	--fragments are produced--
Column 30, line 66:	Page 57, line 17:
"disclosures of which are"	--disclosure of which is--
Column 30, line 67:	Page 57, line 18:
"their entirety."	--its entirety.--
Column 31, line 15:	Page 58, line 3:
"construct allow"	--construct allows--

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Column 31, line 15:	Page 58, line 3:
"construct allow"	--construct allows--
Column 45, line 64:	Page 85, line 12:
"may be proceeded with"	--may be preceded with--

Column 56, lines 8-9:	Page 104, lines 16-17:
"Valadon P., et al., Lucas A. H.; Lucas A. H., 1994;"	--Valadon P., et al., 1996; Lucas A. H., 1994;--
Column 63, line 49:	Page 119, line 1:
"sufficent"	--sufficient--
Column 63, lines 61-62:	Page 119, line 10:
"SP6 to generate"	--SP6 polymerase to generate--
Column 64, lines 1-2:	Page 119, line 15:
"WO 92/18522 the European"	--WO 92/18522 and in the European--
Column 69, line 10:	Page 129, line 7:
"and PAPAP"	--and a PAPAP--
Column 69, line 11:	Page 129, lines 7-8:
"obtaining described herein."	--obtaining them are further described herein.--
Patent Reads:	**Application Should Read:**
Column 69, line 38:	Page 130, line 1:
"devloping"	--developing--
Patent Reads:	**Application Reads:**
Column 72, line 60:	Page 136, lines 8-9:
"(DSM-IV)"	--(DSM-IV) classification.--

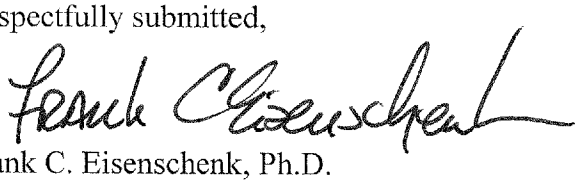
Patent Reads:	**Application Should Read:**
Column 91, line 61:	Applicants' Supplemental Amendment dated October 6, 2006 (original claim 14, subsection c, renumbered as claim 1):
"encodes a polypeptide binds"	--encodes a polypeptide that binds--.

A true and correct copy of pages 25, 101, 104, 119, 129 and 136 of the specification as filed which supports Applicants' assertion of the errors on the part of the Patent Office accompany this Certificate of Correction.

The fee of $100.00 was paid at the time this Request was filed. The Commissioner is also authorized to charge any additional fees as required under 37 CFR 1.20(a) to Deposit Account No. 19-0065.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,



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FCE/yvs/sl

Attachments: Certificate of Correction
Copy of pages 25, 101, 104, 119, 129 and 136 of the specification

(2) BLASTN compares a nucleotide query sequence against a nucleotide sequence database;

(3) BLASTX compares the six-frame conceptual translation products of a query nucleotide sequence (both strands) against a protein sequence database;

(4) TBLASTN compares a query protein sequence against a nucleotide sequence database translated in all six reading frames (both strands); and

(5) TBLASTX compares the six-frame translations of a nucleotide query sequence against the six-frame translations of a nucleotide sequence database.

[0075] The BLAST programs identify homologous sequences by identifying similar segments, which are referred to herein as "high-scoring segment pairs," between a query amino or nucleic acid sequence and a test sequence which is preferably obtained from a protein or nucleic acid sequence database. High-scoring segment pairs are preferably identified (i.e., aligned) by means of a scoring matrix, many of which are known in the art. Preferably, the scoring matrix used is the BLOSUM62 matrix (Gonnet et al., 1992; Henikoff and Henikoff, 1993). Less preferably, the PAM or PAM250 matrices may also be used (see, e.g., Schwartz and Dayhoff, eds., 1978). The BLAST programs evaluate the statistical significance of all high-scoring segment pairs identified, and preferably selects those segments which satisfy a user-specified threshold of significance, such as a user-specified percent homology. Preferably, the statistical significance of a high-scoring segment pair is evaluated using the statistical significance formula of Karlin (see, e.g., Karlin and Altschul, 1990).

[0076] The BLAST programs may be used with the default parameters or with modified parameters provided by the user.

protein is brought into contact with the corresponding purified PAPAP protein, for example the corresponding purified recombinant PAPAP protein produced by a recombinant cell host as described hereinbefore, in order to form a complex between this protein and the putative ligand molecule to be tested.

[0309] As an illustrative example, to study the interaction of the PAPAP protein, or a fragment comprising a contiguous span of at least 6 amino acids, preferably at least 8 to 10 amino acids, more preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 amino acids of SEQ ID No 2, with drugs or small molecules, such as molecules generated through combinatorial chemistry approaches, the microdialysis coupled to HPLC method described by Wang et al. (1997) or the affinity capillary electrophoresis method described by Bush et al. (1997), the disclosures of which are incorporated by reference, can be used.

[0310] In further methods, peptides, drugs, fatty acids, lipoproteins, or small molecules which interact with the PAPAP protein, or a fragment comprising a contiguous span of at least 6 amino acids, preferably at least 8 to 10 amino acids, more preferably at least 12, 15, 20, 25, 30, 40, 50, or 100 amino acids of SEQ ID No 2, may be identified using assays such as the following. The molecule to be tested for binding is labeled with a detectable label, such as a fluorescent , radioactive, or enzymatic tag and placed in contact with immobilized PAPAP protein, or a fragment thereof under conditions which permit specific binding to occur. After removal of non-specifically bound molecules, bound molecules are detected using appropriate means.

[0311] Another object of the present invention comprises methods and kits for the screening of candidate substances that interact with PAPAP polypeptide.

[0312] The present invention pertains to methods for screening substances of interest that interact with a PAPAP protein or one fragment or variant thereof. By their capacity to bind covalently or non-covalently to a PAPAP protein or to a fragment or variant

polypeptides. When the candidate substance or molecule comprises a polypeptide, this polypeptide may be the resulting expression product of a phage clone belonging to a phage-based random peptide library, or alternatively the polypeptide may be the resulting expression product of a cDNA library cloned in a vector suitable for performing a two-hybrid screening assay.

[0320] The invention also pertains to kits useful for performing the hereinbefore described screening method. Preferably, such kits comprise a PAPAP polypeptide or a fragment or a variant thereof, and optionally means useful to detect the complex formed between the PAPAP polypeptide or its fragment or variant and the candidate substance. In a preferred embodiment the detection means comprise a monoclonal or polyclonal antibodies directed against the corresponding PAPAP polypeptide or a fragment or a variant thereof.

A. Candidate ligands obtained from random peptide libraries

[0321] In a particular embodiment of the screening method, the putative ligand is the expression product of a DNA insert contained in a phage vector (Parmley and Smith, 1988). Specifically, random peptide phages libraries are used. The random DNA inserts encode for peptides of 8 to 20 amino acids in length (Oldenburg K.R. et al., 1992; Valadon P., et al., 1996; Lucas A.H., 1994; Westerink M.A.J., 1995; Felici F. et al., 1991). According to this particular embodiment, the recombinant phages expressing a protein that binds to the immobilized PAPAP protein is retained and the complex formed between the PAPAP protein and the recombinant phage may be subsequently immunoprecipitated by a polyclonal or a monoclonal antibody directed against the PAPAP protein.

[0322] Once the ligand library in recombinant phages has been constructed, the phage population is brought into contact with the immobilized PAPAP protein. Then the preparation of complexes is washed in order to remove the non-specifically bound recombinant phages. The phages that bind specifically to the PAPAP protein are then eluted

[0368] The antisense nucleic acids should have a length and melting temperature sufficient to permit formation of an intracellular duplex having sufficient stability to inhibit the expression of the PAPAP mRNA in the duplex. Strategies for designing antisense nucleic acids suitable for use in gene therapy are disclosed in Green et al., (1986) and Izant and Weintraub, (1984), the disclosures of which are incorporated herein by reference.

[0369] In some strategies, antisense molecules are obtained by reversing the orientation of the PAPAP coding region with respect to a promoter so as to transcribe the opposite strand from that which is normally transcribed in the cell. The antisense molecules may be transcribed using in vitro transcription systems such as those which employ T7 or SP6 polymerase to generate the transcript. Another approach involves transcription of PAPAP antisense nucleic acids in vivo by operably linking DNA containing the antisense sequence to a promoter in a suitable expression vector.

[0370] Alternatively, suitable antisense strategies are those described by Rossi et al.(1991), in the International Applications Nos. WO 94/23026, WO 95/04141, WO 92/18522 and in the European Patent Application No. EP 0 572 287 A2

[0371] An alternative to the antisense technology that is used according to the present invention comprises using ribozymes that will bind to a target sequence via their complementary polynucleotide tail and that will cleave the corresponding RNA by hydrolyzing its target site (namely "hammerhead ribozymes"). Briefly, the simplified cycle of a hammerhead ribozyme comprises (1) sequence specific binding to the target RNA via complementary antisense sequences; (2) site-specific hydrolysis of the cleavable motif of the target strand; and (3) release of cleavage products, which gives rise to another catalytic cycle. Indeed, the use of long-chain antisense polynucleotide (at least 30 bases long) or ribozymes with long antisense arms are advantageous. A preferred delivery system for antisense ribozyme is achieved by covalently linking these antisense ribozymes to lipophilic

[0405] Alternatively, PAPAP activity may be increased or decreased by the expression of the genes encoding PAPAP or a PAPAP-modulating compound using gene therapy. Examples of vectors and promoters suitable for use in gene therapy are described above. PAPAP activity may also be increased or decreased by preparing an antibody which binds to a PAPAP peptide, a PAPAP receptor or a protein related thereto, as well as fragments of these proteins. Such antibodies may modulate the interaction between PAPAP and a PAPAP receptor or a protein related thereto. Antibodies and methods of obtaining them are further described herein.

[0406] As described above, the present invention provides cellular assays for identifying compounds for the treatment of psychiatric and other diseases. The assays are based on detection of PAPAP expression, measurement of PAPAP protein activity, or based on the determination of other suitable disease endpoints of schizophrenia, bipolar disorder, a related psychiatric disorder, or any of the disorders discussed herein. Compounds for the treatment of psychiatric disease include derivative proteins or peptides which are capable of inhibiting the activity of a wild type PAPAP protein, which may be identified by determining their ability to bind a wild type PAPAP protein. Compounds also include antibodies, and small molecules and drugs which may be obtained using a variety of synthetic approaches familiar to those skilled in the art, including combinatorial chemistry based techniques. Methods of identifying compounds and methods of preparing formulations and administering medicaments are further described herein.

PAPAP in Methods of Diagnosis or Detecting Predisposition to CNS disorders

[0407] Individuals affected by or predisposed to schizophrenia, bipolar disorder or a related disorder, or to any CaM-KII related disorder including memory and learning disorders, may express abnormal levels of PAPAP. Individuals having increased or decreased PAPAP activity in their plasma, body fluids, or body tissues may be at risk of

[0419] Preferred CNS disorders in the methods of the invention are schizophrenia and bipolar disorder. However, the present invention also comprises any of the prevention, diagnostic, prognosis and treatment methods described herein for any of the herein-described disorders. By way of example, related disorders may comprise learning disorders, cognitive disorders, memory disorders, psychotic disorders, mood disorders, autism, substance dependence and alcoholism, mental retardation, and other psychiatric diseases including anxiety, eating, impulse-control, and personality disorders, as defined with the Diagnosis and Statistical Manual of Mental Disorders fourth edition (DSM-IV) classification.

[0420] The invention also relates to a method of determining whether a subject is likely to respond positively to treatment with a medicament. The method comprises identifying a first population of individuals who respond positively to said medicament and a second population of individuals who respond negatively to said medicament. One or more biallelic markers is identified in the first population which is associated with a positive response to said medicament or one or more biallelic markers is identified in the second population which is associated with a negative response to said medicament. The biallelic markers may be identified using the techniques described herein.

[0421] A DNA sample is then obtained from the subject to be tested. The DNA sample is analyzed to determine whether it comprises alleles of one or more biallelic markers associated with a positive response to treatment with the medicament and/or alleles of one or more biallelic markers associated with a negative response to treatment with the medicament.

[0422] In some embodiments, the medicament may be administered to the subject in a clinical trial if the DNA sample contains alleles of one or more biallelic markers associated with a positive response to treatment with the medicament and/or if the DNA

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CERTIFICATE OF CORRECTION

PATENT NO. : 7,220,581

APPLICATION NO.: 10/071,645

DATED : May 22, 2007

INVENTOR : Bernard Bihain, Barbara Bour, Lydie Bougueleret

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 7,
Line 59, "The term "purfied" may" should read --The term "purified" may--.

Column 13,
Line 33, "nucleofide sequence" should read --nucleotide sequence--.
Line 36, "nucleofide sequence" should read --nucleotide sequence--.

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Line 36, "fragments is produced" should read --fragments are produced--.
Line 66, "disclosures of which are" should read --disclosure of which is--.
Line 67, "their entirety." should read --its entirety.--.

Column 31,
Line 15, "construct allow" should read --construct allows--.

Column 45,
Line 64, "may be proceeded with" should read --may be preceded with--.

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Column 46,
Line 4, "are mammal" should read --is mammal--.

Column 47,
Line 35, "the a polynucleotide" should read --the polynucleotide--.
Line 45, "to a a polynucleotide" should read --to a polynucleotide--.
Line 48, "when the a polynucleotide" should read --when the polynucleotide--.
Lines 49-50, "wherein the a polynucleotide" should read --wherein the polynucleotide--.

Column 54,
Line 23, "protein into contact" should read --protein is brought into contact--.
Line 28, "lignand" should read --ligand--.

Column 55,
Line 63, "between PAPAP" should read --between the PAPAP--.

Column 56,
Lines 8-9, "Valadon P., et al., Lucas A. H.; Lucas A. H., 1994;" should read --Valadon P., et al., 1996; Lucas A. H., 1994;--.

Column 63,
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Column 63,
Lines 61-62, "SP6 to generate" should read --SP6 polymerase to generate--.

Column 64,
Lines 1-2, "WO 92/18522 the European" should read --WO 92/18522 and in the European--.

Column 69,
Line 10, "and PAPAP" should read --and a PAPAP--.
Line 11, "obtaining described herein." should read --obtaining them are further described herein.--.
Line 38, "devloping" should read --developing--.

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